



1653  
\$

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: F. Haviv, et al.

Group Art Unit: 1653

Serial No.: 09/703,233

Examiner: David. Lukton

Filed: October 31, 2000

**Certificate of Mailing under 37 CFR §1.8(a):**

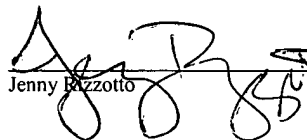
I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being deposited with the United States Postal Service with sufficient postage as First Class Mail addressed to:

For: N-ALKYLATED PEPTIDES  
HAVING ANTIANGIOGENIC  
ACTIVITY

Commissioner for Patents  
Washington, D.C. 20231

Case No.: 6632.US.O2

Date of Deposit: February 12, 2003

  
Jenny Rizzotto Date 2/12/03

TRANSMITTAL LETTER

The Commissioner for Patents  
Washington, D.C. 20231

RECEIVED  
FEB 24 2003  
TECH CENTER 1600/2900

Dear Sir:

Enclosed herewith for the patent application identified above entitled, N-ALKYLATED PEPTIDES HAVING ANTIANGIOGENIC ACTIVITY, are the following:

1. Response to Restriction Requirement;
2. Extension of Time (37 CFR 1.136(a)); and
3. Return Receipt Postcard

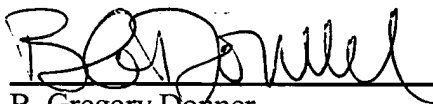
The Commissioner is hereby authorized to charge any additional Filing Fees required under 37 CFR 1.16, as well as any patent application processing fees under 37 CFR 1.17 associated with this communication for which full payment had not been tendered, to Deposit Account No. 01-0025.



23492

ABBOTT LABORATORIES  
Telephone: (847) 937-3810  
Facsimile: (847) 938-2623

Respectfully submitted,  
F. Haviv et al.

  
B. Gregory Donner  
Registration No. 34,580  
Agent for Applicants



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

PATENT

Applicant: F. Haviv, et al.

Serial No.: 09/703,233

Filed: October 31, 2000

For: N-ALKYLATED PEPTIDES  
HAVING ANTIANGIOGENIC  
ACTIVITY

Case No.: 6632.US.O2

Group Art Unit: 1653

Examiner: David. Lukton

**Certificate of Mailing under 37 CFR §1.8(a):**

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being deposited with the United States Postal Service with sufficient postage as First Class Mail addressed to:

Commissioner for Patents  
Washington, D.C. 20231

Date of Deposit: February 12, 2003

Jenny Rizzotto

Date

**RESPONSE TO RESTRICTION REQUIREMENT**  
**AND AMENDMENT A**

Director of Patents and Trademarks  
Washington, D.C. 20231

RECEIVED

FEB 24 2003

TECH CENTER 1600/2900

Dear Sir:

This communication is responsive to the Restriction Requirement dated September 30, 2002, having a period of response through February 28, 2003, pursuant to a four (4) month extension of time under 37 C.F.R. §§ 1.136(a).

Kindly enter this amendment and reconsider the application in view of the accompanying remarks.

Please replace claim 1 with the correspondingly numbered claim.

1 (Amended). A compound having a formula:

Xaa<sub>1</sub>-Xaa<sub>2</sub>-Xaa<sub>3</sub>-Xaa<sub>4</sub>-Xaa<sub>5</sub>-Xaa<sub>6</sub>-Xaa<sub>7</sub>-Xaa<sub>8</sub>-Xaa<sub>9</sub>-Xaa<sub>10</sub>-Xaa<sub>11</sub> (I),  
1 2 3 4 5 6 7 8 9

or a pharmaceutically acceptable salt thereof, wherein

at least one amide bond of an amino acid residue represented by Xaa<sub>3</sub>, Xaa<sub>4</sub>, Xaa<sub>5</sub>,

Xaa<sub>6</sub>, Xaa<sub>7</sub>, Xaa<sub>8</sub>, Xaa<sub>9</sub>, and Xaa<sub>10</sub> is N-alkylated;

Xaa<sub>1</sub> is absent or Xaa<sub>1</sub> is selected from the group consisting of hydrogen, N-methylprolyl, and an acyl group, wherein the acyl group is selected from the group consisting of

$R^1-(CH_2)_n-C(O)-$ , wherein n is an integer from 0 to 8 and  $R^1$  is selected from the group consisting of N-acetylamino, alkoxy, alkyl, aryl, carboxy, cycloalkenyl, cycloalkyl, heterocycle, and hydroxy; and

$R^2-CH_2CH_2-O-(CH_2CH_2O)_p-CH_2-C(O)-$ , wherein p is an integer from 1 to 8 and  $R^2$  is selected from the group consisting of hydrogen, N-acetylamino, and alkyl;

provided that Xaa<sub>1</sub> is absent only when Xaa<sub>2</sub> is N-( $R^3$ )-prolyl;

A1  
Xaa<sub>2</sub> is an N-alkylated amino acid selected from the group consisting of N-( $R^3$ )-alanyl, N-( $R^3$ )-glycyl, N-( $R^3$ )-norvalyl, and N-( $R^3$ )-prolyl, wherein  $R^3$  is C<sub>1</sub>-C<sub>5</sub>-alkyl; or Xaa<sub>2</sub> is an N-unalkylated amino acid selected from the group consisting of

β-alanyl,  
D-alanyl,  
4-aminobutyryl,  
(1R,3S)-1-aminocyclopentane-3-carbonyl,  
(1S,3R)-1-aminocyclopentane-3-carbonyl,  
(1R,4S)-1-aminocyclopent-2-ene-4-carbonyl,  
(1S,4R)-1-aminocyclopent-2-ene-4-carbonyl,  
asparaginy, 3-(4-chlorophenyl)alanyl,  
3-(4-cyanophenyl)alanyl,  
glutaminyl,  
glutamyl,  
glycyl,  
4-hydroxyprolyl,  
3-(4-methylphenyl)alanyl,  
prolyl,  
seryl, and  
threonyl;

Xaa<sub>3</sub> is an N-alkylated amino acid selected from the group consisting of N-(R<sup>3</sup>)-alanyl, N-(R<sup>3</sup>)-glycyl, N-(R<sup>3</sup>)-leucyl, and N-(R<sup>3</sup>)-phenylalanyl, wherein R<sup>3</sup> is as defined above; or Xaa<sub>3</sub> is an N-unalkylated amino acid selected from the group consisting of

alanyl,  
(1S,3R)-1-aminocyclopentane-3-carbonyl,  
(1S,4R)-1-aminocyclopent-2-ene-4-carbonyl,  
asparaginy, l,  
aspartyl,  
3-(3-cyanophenyl)alanyl,  
3-(4-cyanophenyl)alanyl,  
glutaminyl,  
glycyl,  
leucyl,  
lysyl(N-epsilon-acetyl),  
3-(4-methylphenyl)alanyl,  
norvalyl,  
prolyl, and  
phenylalanyl;

Xaa<sub>4</sub> is an N-alkylated amino acid selected from the group consisting of N-(R<sup>3</sup>)-alanyl, N-(R<sup>3</sup>)-glycyl, N-(R<sup>3</sup>)-homophenylalanyl, N-(R<sup>3</sup>)-isoleucyl, N-(R<sup>3</sup>)-leucyl, N-(R<sup>3</sup>)-norvalyl, N-(R<sup>3</sup>)-phenylalanyl, N-(R<sup>3</sup>)-D-phenylalanyl, N-(R<sup>3</sup>)-seryl, N-(R<sup>3</sup>)-tyrosyl, N-(R<sup>3</sup>)-valyl, and N-(R<sup>3</sup>)-D-valyl, wherein R<sup>3</sup> is as defined above; or Xaa<sub>4</sub> is an N-unalkylated amino acid selected from the group consisting of

alanyl,  
alloisoleucyl,  
allylglycyl,  
2-aminobutyryl,  
(1R,4S)-aminocyclopent-2-ene-4-carbonyl,  
asparaginy, l,  
aspartyl,  
3-[2-(5-bromothienyl)]alanyl,  
3-(3-chlorophenyl)alanyl,  
3-(4-chlorophenyl)alanyl,  
3-(3-cyanophenyl)alanyl,

A'

cyclohexylalanyl,  
3-(3,4-dimethoxyphenyl)alanyl,  
3-(3-fluorophenyl)alanyl,  
3-(4-fluorophenyl)alanyl,  
glutaminy,  
glycyl,  
histidyl,  
homophenylalanyl,  
homoseryl,  
isoleucyl,  
leucyl,  
lysyl(N-epsilon-acetyl),  
methionyl,  
methionyl(sulfone),  
3-(4-methylphenyl)alanyl,  
3-(naphth-1-yl)alanyl,  
3-(naphth-2-yl)alanyl,  
norornithyl,  
norvalyl,  
phenylalanyl,  
phenylglycyl,  
prolyl,  
3-(3-pyridyl)alanyl,  
3-(4-thiazolyl)alanyl,  
3-(2-thienyl)alanyl,  
seryl,  
seryl(O-benzyl),  
styrylalanyl,  
tryptyl,  
tyrosyl,  
valyl, and  
D-valyl;

Xaa<sub>5</sub> is an N-alkylated amino acid selected from the group consisting of N-(R<sup>3</sup>)-D-homophenylalanyl, N-(R<sup>3</sup>)-D-isoleucyl, N-(R<sup>3</sup>)-D-leucyl, and N-(R<sup>3</sup>)-D-phenylalanyl, wherein R<sup>3</sup> is as defined above; or Xaa<sub>5</sub> is an N-unalkylated amino

acid selected from the group consisting of

D-alanyl,  
alloisoleucyl,  
D-alloisoleucyl,  
D-2-aminobutyryl,  
D-3-(4-aminophenyl)alanyl,  
D-asparaginyl,  
D-3-(3-benzothienyl)alanyl,  
D-*t*-butylglycyl,  
D-(chlorophenyl)alanyl,  
D-citrullyl,  
D-3-(3-cyanophenyl)alanyl,  
D-cyclohexylalanyl,  
cyclohexylglycyl,  
D-cysteinyl(S-acetamidomethyl),  
D-cysteinyl(S-*t*-butyl),  
D-3-(3,4-difluorophenyl)alanyl,  
D-(3,4-dimethoxyphenyl)alanyl,  
D-glutaminyl,  
glycyl,  
D-homophenylalanyl,  
D-homoseryl,  
isoleucyl,  
D-isoleucyl,  
D-leucyl,  
D-lysyl(N-epsilon-nicotinyl),  
D-lysyl,  
D-methionyl,  
D-3-(4-methylphenyl)alanyl,  
D-3-(naphth-1-yl)alanyl,  
D-3-(naphth-2-yl)alanyl,  
D-3-(4-nitrophenyl)alanyl,  
D-norleucyl,  
D-ornithyl,  
D-penicillaminyl(S-acetamidomethyl),  
D-penicillaminyl(S-benzyl),

A /

D-penicillaminyl(S-methyl),  
D-penicillaminyl,  
D-3-(pentafluorophenyl)alanyl,  
D-phenylalanyl,  
D-prolyl,  
D-seryl(O-benzyl),  
D-seryl,  
D-(2-thienyl)alanyl,  
D-threonyl(O-benzyl),  
D-threonyl,  
D-3-(3-trifluoromethylphenyl)alanyl,  
D-(3,4,5-trifluorophenyl)alanyl,  
D-tryptyl,  
D-tyrosyl(O-ethyl),  
D-tyrosyl, and  
D-valyl;

Xaa<sub>6</sub> is an N-alkylated amino acid selected from the group consisting of N-(R<sup>3</sup>)-aspartyl, N-(R<sup>3</sup>)-glutamyl, N-(R<sup>3</sup>)-glycyl, N-(R<sup>3</sup>)-seryl, N-(R<sup>3</sup>)-threonyl, N-(R<sup>3</sup>)-threonyl(O-benzyl), and N-(R<sup>3</sup>)-tyrosyl, wherein R<sup>3</sup> is as defined above; or Xaa<sub>6</sub> is an N-unalkylated amino acid selected from the group consisting of

alanyl,  
allothreonyl,  
D-allothreonyl,  
allylglycyl,  
asparaginyll,  
aspartyl,  
glutaminyll,  
glycyl,  
histidyl,  
homoseryl,  
D-homoseryl,  
3-(4-hydroxymethylphenyl)alanyl,  
isoleucyl,  
lysyl(N-epsilon-acetyl),  
methionyl,

3-(naphth-2-yl)alanyl,  
norvalyl,  
octylglycyl,  
prolyl,  
3-(3-pyridyl)alanyl,  
seryl,  
D-seryl,  
threonyl,  
D-threonyl,  
tryptyl,  
tyrosyl, and  
tyrosyl(O-methyl);

A /  
Xaa<sub>7</sub> is an N-alkylated amino acid selected from the group consisting of N-(R<sup>3</sup>)-alanyl, N-(R<sup>3</sup>)-glycyl, N-(R<sup>3</sup>)-isoleucyl, N-(R<sup>3</sup>)-leucyl, N-(R<sup>3</sup>)-D-leucyl, N-(R<sup>3</sup>)-norleucyl, N-(R<sup>3</sup>)-norvalyl, N-(R<sup>3</sup>)-seryl, N-(R<sup>3</sup>)-threonyl, and N-(R<sup>3</sup>)-valyl, wherein R<sup>3</sup> is as defined above; or Xaa<sub>7</sub> is an N-unalkylated amino acid selected from the group consisting of

alanyl,  
allothreonyl,  
allylglycyl,  
3-(4-amidophenyl)alanyl,  
2-aminobutyryl,  
arginyl,  
asparaginyll,  
cyclohexylalanyl,  
glutaminyl,  
D-glutaminyl,  
glycyl,  
homoalanyl,  
homoseryl,  
4-hydroxyprolyl,  
leucyl,  
D-leucyl,  
lysyl(N-epsilon-acetyl),  
methionyl sulfone,



methionyl sulfoxide,  
methionyl,  
norleucyl,  
norvalyl,  
D-norvalyl,  
octylglycyl,  
ornithyl(N-delta-acetyl),  
phenylalanyl,  
propargylglycyl,  
seryl,  
D-seryl,  
threonyl,  
tryptyl,  
tyrosyl, and  
valyl;

A1  
Xaa<sub>8</sub> is an N-alkylated amino acid selected from the group consisting of N-(R<sup>3</sup>)-alanyl, N-(R<sup>3</sup>)-D-alanyl, N-(R<sup>3</sup>)-isoleucyl, and N-(R<sup>3</sup>)-leucyl, wherein R<sup>3</sup> is as defined above; or Xaa<sub>8</sub> is an N-unalkylated amino acid selected from the group consisting of

alanyl,  
alloisoleucyl,  
D-alloisoleucyl,  
allylglycyl,  
citrullyl,  
glycyl,  
isoleucyl,  
D-isoleucyl,  
leucyl,  
D-leucyl,  
lysyl(N-epsilon-acetyl),  
D-lysyl(N-epsilon-acetyl),  
methionyl,  
3-(naphth-1-yl)alanyl,  
norvalyl,  
prolyl,

D-prolyl, and  
valyl;

Xaa<sub>9</sub> is the N-alkylated amino acid N-(R<sup>3</sup>)-arginyl, wherein R<sup>3</sup> is as defined above;  
or Xaa<sub>9</sub> is an N-unalkylated amino acid selected from the group consisting of

[(4-amino-N-isopropyl)cyclohexyl]alanyl,  
3-(4-amino-N-isopropylphenyl)alanyl,  
arginyln(N<sup>G</sup>N<sup>G'</sup> diethyl),  
arginyln,  
D-arginyln,  
citrullyln,  
glutaminyl,  
3-(4-guanidinophenyl)alanyl,  
histidyl,  
homoarginyl,  
lysyl(N-epsilon-isopropyl),  
lysyl(N-epsilon-nicotinyl),  
lysyl,  
norarginyl,  
ornithyl,  
ornithyl[N-delta-(2-imidazolinyln)],  
ornithyl(N-delta-isopropyl), and  
3-(3-pyridyl)alanyl;

Xaa<sub>10</sub> is an N-alkylated amino acid selected from the group consisting of N-(R<sup>3</sup>)-  
alanyl, N-(R<sup>3</sup>)-D-alanyl, N-(R<sup>3</sup>)-glycyl, N-(R<sup>3</sup>)-homoalanyl, and N-(R<sup>3</sup>)-norvalyl,  
wherein R<sup>3</sup> is as defined above; or Xaa<sub>10</sub> is an N-unalkylated amino acid selected  
from the group consisting of

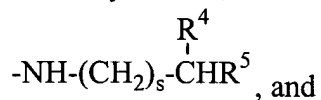
D-alanyl,  
2-aminobutyryl,  
D-2-aminobutyryl,  
2-aminoisobutyryl,  
3,4-dehydroprolyl,  
4-hydroxyprolyl,  
phenylalanyl,  
prolyl,

D-prolyl,  
1,2,3,4-tetrahydroisoquinoline-3-carbonyl, and  
D-valyl; and

Xaa<sub>11</sub> is a hydroxy group or an amino acid amide selected from the group consisting of:

alanylamide,  
D-alanylamide,  
alanylethylamide,  
D-alanylethylamide,  
azaglycylamide,  
glycylamide,  
glycylethylamide,  
lysyl(N-epsilon-acetyl),  
D-lysyl(N-epsilon-acetyl),  
N-methyl-D-alanylamide,  
sarcosylamide,  
serylamide,  
D-serylamide,

a residue represented by the formula



a group represented by the formula  $-\text{NH}-\text{R}^6$ ; wherein

s is an integer from 0 to 8;

R<sup>4</sup> is selected from the group consisting of hydrogen, alkyl, and a 5- to 6-membered cycloalkyl ring;

R<sup>5</sup> is selected from the group consisting of hydrogen, alkoxy, alkyl, aryl, cycloalkenyl, cycloalkyl, heterocycle, and hydroxy;

provided that s is not zero when R<sup>5</sup> is hydroxy or alkoxy; and

R<sup>6</sup> is selected from hydrogen and hydroxy.